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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,997	10/04/2005	Kai Schiemann	MERCK-3071	6470

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
01/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,997	SCHIEMANN ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/4/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-18 are rejected. Claim 12 and 16 are cancelled. Claim 19 is a new claim.

2. Claims 1-11, 13-15, and 17-19 are pending in this application. Claims 12 and 16 have been cancelled. This action is in response to the applicants' amendment after a non-final and reply filed on October 25, 2007.

Status of Objections

4. The specification was objected to as not containing titles to distinguish the separate section of the specification. The objection to the specification is hereby upheld.

5. The specification was objected to for the "incorporation of essential material." Applicants arguments have been found persuasive and the objection of the specification is hereby withdrawn.

6. The specification was objected to for the incorrect nomenclature of a compound. The objection of the specification is hereby withdrawn due to applicant's amendments.

Status of Rejections

7. Claims 16 and 17 were rejected under 35 U.S.C. 101 and U.S.C. 112, first paragraph, as being drawn to "use" claims and not complying with the utility and written description requirement. The rejection of claims 16 and 17 are moot and are hereby withdrawn in light of the cancellation of claim 16 and the applicant's amendments concerning claim 17.

8. Claims 1 and 9 are rejected under 35 U.S.C. 112, second paragraph, as failing to comply with the definiteness requirement. The rejection of the claims is hereby withdrawn due to applicant's amendments.

9. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as failing to comply with the definiteness requirement. The rejection of the claims is deemed moot and hereby withdrawn due to applicant's cancellation of the claim.

10. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement and only showing a scope of enablement. The applicants arguments have not been found persuasive.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds, compositions, derivatives, salts and mixtures thereof does not reasonably provide enablement for forming any polymorphic forms, solvates or stereoisomers listed within Claims 1-19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Morphological forms of the compound, or "polymorphs" are the ability of a substance to exist in two/more crystalline phases that have different arrangement and/or conformation of molecules in a crystal lattice.

Screening of pharmaceuticals early on in drug discovery to find out all possible solid forms has significant connotations. (Chawla et. al.; Current Research & Information on Pharmaceutical Science, 2004, 5(1), p. 9, col.2, para.1) When designing formulations, it is imperative to know which crystal form of a drug is present at the various stages of a process. "It may be possible that if one polymorph of an active pharmaceutical ingredient, or API, is responsible for activity, another form may be less active, inactive, toxic, or have some other properties of interest." (Chawla et. al.; p. 9, col.2, para.3)

Polymorphs can exhibit many types of differences in their physical properties such as a) packaging; b) thermodynamic; c) spectroscopic; d) kinetic; e) surface; and, f) mechanical properties. (Chawla et. al.; See Table 1, p. 10) These properties offer scientists the opportunity to manipulate bioavailability. It is important to determine if there are phase transformations occurring during

processing as well as what crystal form is present in the final drug product. (Newman et. al.; Drug Discovery Today, 2003, 8(19) p. 898, col.2, Para.3).

The scope of "solvate" and "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be predicted and there fore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. (Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

"Stereoisomers" literally would include thousands of additional compounds covered by the claims' scope that has the same molecular formula. In the absence of any guidance in the specification, nothing short of extensive synthesis and testing would be needed to determine if any such "isomeric" compound would have the activity needed to practice the invention.

2) *Amount of guidance provided by Applicant*. While the Applicant has demonstrated within the application how to make the compounds of Formula I, the applicant has not shown any useful data or guidance that would define a particular polymorph, solvate or stereoisomer that would be biologically active.

The applicant has inferred within the specification that these would be acceptable. This can clearly not be the case. A contrasting example to this would be chloramphenicol palmitate (CAP). CAP exists in a form A and B. The metastable "form B" of CAP has an eight-fold higher bioactivity than "form A." Yet if "form B" is administered to humans, it can cause potentially fatal side effects. (Chawla et. al.; p. 9-10). Also a variety of dosage forms are available for pharmaceutical products. (Newman et. al.; p. 899, col.2, Box 1) A polymorph can affect the key solid-state parameters. For example, the drug substance in a tablet formulation will be significantly different than those for an oral suspension or inhalation product. (Newman et. al.; p. 898, col.2, Para.1)

3) *Number of working examples.* Applicant has provided no detailed working examples of various polymorphs, solvates, or stereoisomers in the current application.

4) *Nature of the invention.* The application relates to chromenoneindoles of the formula I and and pharmaceutically usable prodrugs, derivatives, solvates, stereoisomers and salts thereof, including mixtures thereof in all ratios.

5) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. or M.S. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention

without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

Conclusion

11. Claims 1-11, 13-15, and 17-19 are rejected.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Examiner, Art Unit 1624

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